II. Remarks

A. Formal Matters

Claims 10-12 are withdrawn from consideration in light of the species election but should be rejoined upon a finding of allowability of claim 9. Applicants respectfully submit that claim 9 is patentable as explained *infra*, and its patentability does not depend on the species elected as claimed in claim 13. Accordingly Applicants hereby request rejoinder of the species in claims 10-12.

Applicants herein amend the paragraph beginning at page 73, line 20 of the specification to correct a typographical error.

Applicants herein amend the paragraph beginning at page 73, line 25 of the specification to correct typographical errors.

Applicants herein amend the abstract and respectfully request reconsideration and withdrawal of the Examiner's objection thereto (*see* page 4 of the Office Action).

In view of the application as originally filed providing support for each of the amendments made herein, Applicants respectfully submit that no new matter has been added.

B. The Information Disclosure Statement Filed March 18, 2004 Complies With 37 C.F.R. §1.98

At page 3 of the Office Action, the Examiner alleges that the information disclosure statement filed March 18, 2004 (hereinafter "the IDS") fails to comply with 37 C.F.R. §1.98(a)(2) and therefore has not considered the information referred to therein. Applicants respectfully submit that the IDS is proper and in full compliance with 37 C.F.R. §1.98. According to 37 C.F.R. §1.98(d), copies of the references identified on an IDS need not be submitted where copies were properly submitted to the Office in an earlier application identified on the IDS and relied on for an earlier effective filing date under 35 U.S.C. §120. The declaration filed with the instant application states that copies of the references contained in the IDS are on file for U.S. Application No. 09/726,219 (hereinafter the "'219 Application"), the parent application from which the instant Application claims priority under 35 U.S.C. §120. The Examiner acknowledges that the art cited in the IDS was "found in prior applications" including the '219 Application.

A petition to expunge certain references in the '219 Application was granted on June 9, 2004. However, a supplementary IDS was filed on October 20, 2004 in connection with the instant Application, on which the expunged references were listed and legible copies of the expunged references submitted therewith. Accordingly, Applicants respectfully submit that the IDS filed March 18, 2004 is proper and hereby request that the Examiner consider each reference therein.

C. The Objections to the Drawings Should be Withdrawn

At page 4 of the Office Action, the Examiner objects to Figures 4a, 10a, 10b, 10c, 16b, 24a, 24b, 44a, 44b and 52 which contain sequences listed in the sequence listing, allegedly because "tables and sequence listings included in the specification must not be duplicated in the drawings." Applicants direct the Examiner's attention to MPEP §2422.02 which states, in relevant part, "[i]n view of the fact that many significant sequence characteristics may only be demonstrated by a figure, the exclusive conformance requirement of this section may be relaxed for drawing figures." A few representative examples are provided in which the conformance requirement is to be relaxed, including the depiction of nucleotides featuring "sticky ends," sequence alignments, and depiction of protein structural features. However, the examples provided "are given by way of example only and there may be many other reasons for relaxing the requirements of this section for the drawing figures." MPEP §2422.02. Applicants respectfully submit that the requirements should be relaxed in the instant case. First, the aforementioned figures are not merely reproductions of the sequence listing; rather, each figure provides additional information about the specific subset of sequences therein which is most logically provided in the form of a drawing. Figure 4a groups together the oligonucleotides used for the *in vitro* mutagenesis (and subsequent sequencing) of the FDTδBst vector to create the FDTPs/Xh vector (see Figure 3), thus removing the need for the skilled artisan to hunt through the lengthy specification to retrieve the information. Figures 10a, 10b and 10c depict an alignment of the nucleotide sequence encoding VL of Fab D1.3 with the encoded amino acid sequence. Figure 16b depicts an alignment of linker sites within region gene III (depicted in Figure 16a) for insertion of a BamH1 site. Figures 24a and 24b depict alignments of VH and VK gene sequences derived from a combinatorial library and mark the CDR sequences. Figures 44a and 44b depict an alignment of the nucleotide sequence encoding scFvB18 with the encoded

amino acid sequence. Figure 52 depicts an alignment of the nucleotide sequences of light chains D1.3, M1F and M21 derived by selection from a hierarchical library. In view of the information provided by the aforementioned figures beyond that provided by the sequence listing, Applicants hereby request reconsideration and withdrawal of the objections.

D. Patentability Arguments

1. **The Rejections Under 35 U.S.C. §102(e) Should be Withdrawn**

At page 6 of the Office Action, the Examiner rejects claims 9 and 15-17 under 35 U.S.C. §102(e), as allegedly anticipated by U.S. Patent 5,427,908 (hereinafter "Dower"). The Examiner cites against claim 9, the "abstract; columns 1-12; Example 1; claims 1-4 and 7-17" of Dower, which the Examiner characterizes as teaching methods for displaying binding domains of antibodies including antibody fragments, VH and VL on phage surface and screening the phage to select a specific binding domain. To anticipate a claim, a reference must teach each and every element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The pending claims of the instant application require that the binding domain of the binding molecules consists of a dAb fragment. The abstract of Dower, however, refers only to "proteins of interest" and "novel proteins such as monoclonal antibodies." There is no disclosure of dAbs at all. The claims of Dower are directed to screening a DNA library for nucleotide sequences which encode "an antibody Fab fragment comprising first and second polypeptide chains, one chain comprising a light chain variable region and another chain comprising a heavy chain variable region." Clearly, as was well known in the art, Fab molecules are not the same as dAbs. Example 1 of Dower is similarly directed to display of Fab molecules, in which one polypeptide chain composed of VH and CH domains is presented as a fusion with bacteriophage gene III protein and displayed with an associated second polypeptide composed of VL and CL domains to provide a binding domain formed by the VH and VL domains together.

Dower is concerned with provision of multichain proteins in general and Fab molecules in particular, as reflected throughout columns 1-12. Each mention of VH and VL chains throughout Dower is for the identification and cloning, with it being explicitly stated that it is "the binding fragments (Fv) or Fab encoded thereby" that are to be employed, i.e., multichain proteins in which VH and VL domains associate to form a binding domain. *See* for example,

Dower, column 3, lines 28-41. The cloning of VH and/or VL domains is further elaborated at Dower, column 4, lines 51-64 where the use of separate cloning vectors for antibody light and heavy chain sequences is suggested from which a combinatorial library is constructed to bring together VH and VL domain sequences in pairs associated to form binding domains. Moreover, in relation to column 4, Applicants direct the Examiner's attention to the fact that this is in relation to use of bacteriophage lambda, which is a lytic phage assembled intracellularly and not a filamentous bacteriophage as required by the instant claims. Furthermore, the reference is explicitly to expression, not display and citation is given to Huse *et al.*, Science 246:1275-1281 (1989) and Short *et al.*, Nucleic Acids Res. 16:7583 (1988), both of which are concerned with expression from lambda vectors and not bacteriophage display. Thus, Dower relates to display of multichain proteins, mostly Fab, with a suggestion of Fv, and not dAbs as required by the present claims. Accordingly, Applicant respectfully submits that claims 9 and 15-17 are in condition for allowance and hereby requests withdrawal of the rejections under U.S.C. §102(e).

2. **The Rejection Under 35 U.S.C. §103 Should be Withdrawn**

At page 7 of the Office Action, the Examiner rejects claim 9 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 90/02809 (hereinafter "Ladner and Guterman") and WO 88/06630 (hereinafter "Ladner *et al.*"). The Examiner characterizes Ladner and Guterman as teaching display of binding domains, encoded by nucleic acid sequences, on the surface of filamentous bacteriophage and screening via binding to targets. The Examiner further characterizes Ladner and Guterman as failing to expressly convey the expression of antibody fragments on the surface of filamentous phage. The Examiner characterizes Ladner *et al.* as teaching methods of displaying SCADs or single-chain antibodies on the surface of Lambda phage and screening against antigens. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made "to alter the methods of screening filamentous phage displaying proteins of Ladner and Guterman with the SCADs or antibody fragments of Ladner et al."

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981 (CCPA 1974). The Examiner's rejection of claim 9 under 35 U.S.C. §103(a) relies on the Examiner's belief that Ladner *et al.* discloses use of molecules that are an essential component of the present

claims, i.e. that Ladner *et al.*'s "SCADs" equate to dAbs. In fact, the "SCADs" of Ladner *et al.* are more commonly known as scFv or single-chain Fv molecules which consist of a VH domain and a VL domain joined by a peptide linker so that the binding domain is composed of the VH and VL domain. In dAbs, only a VH domain or a VL domain is present to form the binding domain. In other words, the present invention is concerned with different molecules from those of Ladner *et al.*

The nature of the SCAD's of Ladner *et al.* can be understood from the material presented in Ladner *et al.* as the source of the term, i.e., copending U.S. Patent Application No. 10/902,970. U.S. Patent Application 10/902,970 issued as U.S. patent 4,704,692 (hereinafter the "'692 patent"). The '692 patent teaches a method for "generating single chain structures from two-chain aggregate structures, wherein the single chain will retain the three-dimensional folding of the separate natural aggregate of two polypeptides chains." See '692 patent, column 2, lines 31-35. One of ordinary skill in the art would understand that the '692 patent teaches the creation, in a single polypeptide chain, of a replica of an Fv molecule, which is a two-chain molecule consisting of a VH domain and a VL domain associating to form a single binding domain. *See* also, e.g., '692 patent, figures 6B and 7. Similarly, claim 1 of U.S. Patent No. 5,260,203, which issued from a successor application to 10/902,970, covers:

> A single chain polypeptide having binding affinity for a given antigen, said polypeptide comprising:
>
> (a) a first polypeptide comprising the antigen binding portion of the light chain variable region of an antibody;
>
> (b) a second polypeptide comprising the antigen binding portion of the heavy chain variable region of an antibody; and
>
> (c) at least one peptide liner (sic) linking said first and second polypeptides (a) and (b) into a single chain polypeptide having binding affinity for said given antigen.

Accordingly, the combination of Ladner and Guterman with Ladner *et al.* does not teach or suggest every limitation of the present invention as claimed, which requires the display of binding molecules of which the binding domain consists of a dAb, and therefore cannot render claim 9 obvious. Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

3. **The Rejections Based On Nonstatutory Double Patenting Should be Withdrawn**

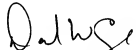
At pages 8-15 of the Office Action, Examiner rejects various claims of the present Application under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent Nos. 5,969,108; 5,885,793; 6,521,404; 6,555,313; 6,582,915, 6,544,731, 6,593,081 and 6,916,605; and copending U.S. Patent Application No. 10/803,653. In order to expedite the allowance of the present Application and without in any way acknowledging agreement with the Examiner's statement with respect to the claims of the present Application, Applicants submit terminal disclaimers herewith. Therefore, the rejections are moot and should be withdrawn.

E. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

By: 
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Dated: December 22, 2006

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